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THE SO-CALLED «IDIOPATHIC MYOCARDITIS»

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by

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Myocarditis today consits of the well defined group as diphtheritic, rheumatic, syphilitic and tuberculous with typical tuberles; other less well known groups associated with influenza, Chaga's disease, other trypanosomiasis, whooping cough etc. and lastly cases with obscure origins which were first described by *Fiedler* in 1899 and are now generally known as *Fiedler's* isolated myocarditis. Although nearly a half century has passed this so-called *Fiedler's* isolated myocarditis is still like febrile diseases about a century ago with an unknown cauative agent, which no doubt are of many. Therefore the term *Fiedler:s* isolated myocarditis or idiopathic myocarditis at present is simply a waste paper basket containing every case of which the origin is not clear.

In dealing with myocarditis the difficulty of diagnosis is very obvious. Although clinicians sometimes would think of the possibility of myocarditis in the course of diseases when the patient suddenly becomes worse with rapid pulse, dyspnea, sometimes angina, low voltage of QRS complex and inverted T waves in one or all the leads he is still very skeptical in making such a diagnosis because so many other conditions can cause such changes, for instance, anoxemia of the myocardium or toxic degeneration of the cardiac muscle fibers in infectious diseases. Moreover the EKG alternations are not evident in all cases nor continually in those demonstrable cases. They develope either when foci of inflammation exist at definite places, for example, the His Bundle, atrioventricular node or in one of the major conduction branches or when the involved area is large enough to show change in the tracing. However on the other hand when there is no clinical finding suggesting the possibility of myocarditis

yet on postmortem and under with microscope very marked diffuse myocarditis may be seen. There is no other disease in medicine than myocarditis that so much discrepancies exist in between clinical and pathological diagnosis. The controversy has been mentioned by many leading cardiologists as *Rothschild*[1] who states that disturbance of functions were found to occur without demonstrable morphologic change, clinicians became more discerning and attempted to analyze more closely what part of the circulatory mechanism is at fault and the diagnosis of myocarditis became less frequent and prophetically will become even less frequent. *Christian*[2] also in his discussion of myocarditis said that if acute myocarditis is meant an actual inflammatory process of the myocardium with infiltration of polymorphonuclear leucocytes it is a rare condition and consequently of minor clinical importance. On the other hand, if by acute myocarditis is meant the circulatory disturbance, with or without evidence of degeneration of the muscle fibers or cellular infiltration between them, associated with acute infectious diseases, it is a frequent occurance.

However the pathologist is sure to make a diagnosis of myocarditis under microscope when either evidence of cellular infiltration which may be of different kinds or degeneration of muscle fibers or granulation tissue is present. This diagnosis is made whether there is or no clinical support. Therefore the diagnosis of this malady between clinicians and pathologists can coincide only when better methods of clinical diagnosis have developed.

Fiedler's isolated myocarditis or idiopathic myocarditis according to *Magner*[3] and *Hannsmann* and *Schenken*[4] and supported by *Candel* and *Wheelock*[5], consists of a heterogenous group, including atypical varieties associated whith tuberculosis, syphilis, rheumatic fever and disorder of unknown origin. According to the Scandinavian author, Bertel von *Bonsdorff*[6], many of the reported *Fiedler's* or idiopathic myocarditis should be included under the heading of myocardial disease of obscure origin of which the author reported 8 cases. It had been published in the continental literature since 1899 by *Fiedler* and followed by many others including *Sellentin*,[7] *Saltykow*,[8] *Sikl*,[9] *Kaufmann*[10] and others. In America it was first called to attention by *Saphir*[11] who reviewed this subject in 1929 and collected 36 cases from the literature including two of his own. *Helwig* and *Wilhelmy*[12] while reporting three cases of this disease mentioned that in 1935 *Simon* and *Walpaw* recorded 48 cases from the literature and added one of his own in which focal interstitial myocarditis as the cause of death and since then *Scott* and *Simon*, *Hirai* and *Kjaergaard* have reported a single case making a total of 52 cases in the literature up to 1938 which have been proved by necropsy. Since then more cases have been reported both clinically and pathologically and will be mentioned in later discussion.

Classification

Classification is obviously difficult because of the obscure origin and bizzarre clinical manifestations of this disease. Since the origin is not clear at present the classification surely will be best based upon the pathological picture.

1. Cellular infiltration with round cells, polymorphonuclear leucocytes, plasma cells, histiocytes and as well as eosinophiles. This of course comprises most of the reported cases in the literature. In this group dispute arises concerning about the origin of the cellular infiltration. *Hannsmann* and *Schenken*[4] and *Covey*[17] had presented evidence that the process begins with damage of the myocardial fibers but very recently *Marcuse*[13] in reviewing 36 cases of non-specific myocarditis had found evidence that the inflammatory process seems to have originate in the interstitial connective tissue and any involvement of the muscle fibers were apparently of secondary nature and this impression was enhanced by examination of the group classified as «minimal myocarditis» in which the lesions were found exclusively within the fibrous tissue septums.

2. Giant cell formation: This includes cases with giant cell formation besides the cellular infiltration. *Saltykow*[8] as early as 1905 in this institute had described the elongated form of giant cell in one of his two cases of isolated myocarditis, but it was nine years later when he [14] published his second paper that he proposed the term «specific productive myocarditis» for the case he reported of a 28 year old housewife who died suddenly while sleeping. Besides the usual picture of isolated myocarditis the most unusual finding is the presence of many giant cells sometimes 50—70 in one field which he believed are from the regeneration of muscle fibers. Since then more cases with this pathological picture appeared in the literature including *Baumgartner's*[15] cases which were subdivided by the author into

a) with necrosis and cellular infiltration only
b) without necrosis or giant cell but cellular infiltration only,
c) both cellular infiltration, necrosis and giant cell and
d) with cellular infiltration and giant cell but no necrosis.

Gierke's[16] one case, a 25 year old maid who also died suddenly, had the same pathological picture. More recently *Sikl*[9] reported two cases of this type in 1936. Both had heart failure after developing exfoliative dermatitis which was the result of bismuth and neoarsphenamine treatment for their syphilis. *Magner*[18] reported another case in 1939 after thyroidectomy and again *Saphir*[19] added one more case in 1942 of a 40 year old man who died suddenly while working. *Sampson*[20] also reported a case of 38 year old woman who also succumbed suddenly while sleeping and on

microscopic examination cells of granulomatous type were occasionally seen. It is in this group that the question arises whether or not some instances of the granulomatous myocarditis may be the result of one of the known inflammatory processes especially tuberculosis and syphilis although neither tubercle bacilli nor treponema pallidium can be demonstrated and the Wassermann and Kahn tests are negative. Moreover *Saphir*[19] had found small granulomatous lesions in the myocardium in one case in which trichinella spiralis was encountered in the diaphragm and histologically the changes in the myocardium ressemble very much those of granulomatous myocarditis and diffuse isolated myocarditis.

3. The third group consists of the so-called serious type with interstitial edema and also the myofibrosis type in which there is very marked fibrous tissue formation replacing the degenerated muscle fibers with very little or no cellular infiltration. *Rössle*[21] *in* 1934 while reporting cases with interstitial edema in various organs including liver, heart, adrenal and hypophysis termed this change in the heart as serous myocarditis without any infections cellular elements which may be followed by fibrosis. He pointed out that the nature of this change is not very clear and of many origins, may be toxic in origin or a milder form of infection in the myocardium. The same kind of change in myocardium was reported by *Francz*[22] in 1937 in a patient who had been suffering from bronchial asthma and received constant injections of adrenalin. Under the microscope there were primary degeneration of muscle fibers with vacuolization and also fibrous tissues, young fibroblasts and few lymphocytes interstitially. The author produced the same change in the myocardium among animals by the injection of adrenalin and caffeine and he mentioned that as early as 1909 *Fleisher*[23] and Loeb had found 59% of animals receiving injections of caffeine and adrenalin had developed similiar myacarditis. A year later in 1938 *Lindberg*[24] reported that one of his tho cases, who was a child, had a cough at the 7th month and died four months later with a sudden onsed of dyspnea. The wohle heart especially the left ventricle had a marked disappearence of muscle fibers and was filled more or less with fibrous tissue. The longitudinal as well as the transverse striations were not distinct with pyknotic nuclei. The degenerated muscle fibers had vacuolization and loss of sarcoplasm. Interstitial edema was found in between the heart muscle fibers especially in the papillary muscle of the left ventricle. Only in one small focus cellular infiltration with fibroblasts, lymphocytes, histiocytes, neutrophiles and eosinophiles could be found. In *Bonsdorff's*[6] 8 cases of myocardial disease of obscure origin there were at least 5 with fibrosis of the myocardium and vacuolization of muscle fibers, which were widely separated but he still considered them as myocarditis. This type of change will be described again in connection with burns, under etiology.

Etiology:

As had been stated above the origin of this disease is of manifold and sometimes obscure. Sometimes the etiology can be traced, and believed most probably to be so, but many times we can only speculate. Besides the granulomatus type, in which although cousative organisms can:t be demonstrated but believed to be connected with tuberculosis, syphilis etc. by several authors, the rest of cases can be grouped under four headings.

1. Upper respiratory infection and other viral diseases. «cold» had often been mentioned in connection with isolated myocarditis by many authors including *Wassmann's*[25] one case, *Smith* and *Stephen's*[26] 2 cases, *Kjaergarrd's*[27] 4th and 5th cases, *Scott* and *Saphir's*[11] one case in 1929 and also one of *Saphir's*[19] 12 cases reported in 1942. In *Bonsdorff's*[6] *8 cases* of myocardial disease of obscure origin there were three with the same history and he rightly pointed out that the above mentioned cases were truely the so-called «isolated acute myocarditis» because the «cold» might be just a mild form of influenza which had been reported by *Schmorl*[28] in 1919 and *Roulet*[29] in 1935 (5 and 2 cases respectively) to cause true myocarditis. In connection with this it should be mentioned that *Saphir*[30] reported 5 cases of early acute laryngotracheobronchitis that died suddenly with myocarditis. Mumps had been reported by *Wendkos* and *Noll*[31] as causing myocarditis with the manifestation of prolongation of the P-R interval which became normal after convalescence. This author also cited that involvement of the heart in mumps with acute interstitial myocarditis by a fibrinous exudate can differentiate it from other forms of myocarditis. *Pearce* and *Lange*[32] by injecting various substances such as barium chloride, epinephrene, betahypophamine and acacia causing anocia of the myocardium through various mechanisms and also by decreasing the percentage of otygen in the animal's breathing air were able to increase the percentage of carditis including myocarditis in rabbits by inoculating pseudorabies virus from 16.1% to 50—100% as compared with controls which received injections of the same virus and various substances such as corn syrup, nikethamide, digitalis, chloroform or papaverine which are not supposed to interfere with the oxygen supply of the heart. In *Pearcy's*[33] earlier report he observed that several kinds of virus such as vaccine virus, fibroma virus (inflammatory and A strains) and myxoma virus could also cause carditis in rabbits which varied from 20—60% and this was also increased by injecting acacia. More recently *Schmidt*[34] had isolated a virus from the second of three animals (first one is a gibbon and the 2nd and 3rd are chimpanzees) that died of myocarditis (2 suddenly and one sick for 5 days) with hydrothorax and pericarditis.

Microscopically there were minute foci of necrosis with cellular infiltration. Mice were most susceptible to this isolated virus with paralysis on the 4—5th day and death from 7 to 10 days but in the ater passage some might live as long as 37 days. The earliest finding in the inoculated animals was perivascular monocytic infiltration followed by necrosis on the 6th day which became more extensive with the appearence of fibroblasts and monocytes. The calcification started on the 10th day and after the 20th day fibroblastic replacement and calcification were often the remnants of the disease. Guinea pigs and Hampsters were also susceptible but rabbits slightly. In the inoculated animals lesions such as myelitis, encephalitis, hyperemia and edema of lungs and interstitial nephritis were seen. The control group was not affected. The most significant thing is the foot note of this paper which stated that recently *Smadel*[35] reported that stored frozen sera collected from a group of soldiers with «3 days fever» in Manila in December 1945 gave positive results in neutralization test for this agent. During the course of the illness the antibody titre increased and was highest during convalescence. In view of all the facts we incline to believe that many cases of idiopathic diffuse myocarditis having symptoms of upper respiratory infection or « cold » might well be due to certain type of virus. More research should be done along this line before any conclusion can be drawn.

2. Burns and suppurative processes of the skin and oral cavity. *Saltykow* in his paper reported the cases of idiopathic myocarditis; the first had an operation for tuberculous lymphadenitis and the other had burns which had healed before the patient suddenly died. The author also mentioned that *Sellentin's* case had carbuncles and two of *Fiedler's* four cases had ulcers on the lower extremities. *Kaufmann*[10] in discussing idiopathic myocarditis also mentined that the etiology is manifold: «pathological conditions of the skin such as my own case with abscesses after burns. In another group there was infection in the operative field after the tuberculous lymph gland in the neck was removed. In *Wolff's* case trauma of the elbow and in *Aschoff's* case trauma of the hand was present — and also *Zuppinger's* case of a child had suppurative infection of the foot.» *Bernheim-Karrer* [36 37] had reported repeatedly in 1905 and 1923 the relationship of eczema with inflammatory cellular infiltration in the myocardium although in his first paper he didn't attribute the cause of death to it. *Maslow* and *Lederer's*[38] case also had repeated tonsillitis in the past and stomatitis and blepharitis shortly before the onset of cardiac failure and death. Recently acute otitis media had been mentioned as the cause in none of the two cases reported by *Wassmann*[25] althoug the diagnosis is only clinical. In the last case reported by *Smith*

and *Stephens*[26] which was also diagnosed clinically, there was also a history of an infected finger and lymphadenitis two months before the onset of cardiac failure, *Maxwell* and *Barrett*[39] reported a 53 year old man who developed signs and symptoms of cardiac failure after developing dermatitis which was the result of sulfur treatment for his scabies with fever, a leucocytic count of 15,700 and 93 % polymorphonuclear leucocytes. The authors believed the acute interstitial myocarditis diagnosed by both gross and microscopic examination, was due to dermatitis although the patient also had acute pharyngitis at the time when he had cardiac failure. Polymyositis had been attributed as one of the causes by *Zalka*[40] who reported one such case. *Glatthaar*[41] here reported 28 cases with focal infection (two of dental origin, one of chronic parasinusitis and the rest of tonsillitis) who had EKG tracing as before and after operation. 15 of them had EKG tracings and 5 had subjective improvement after the operation to suggest the presence of myocarditis. The diagnosis of myocarditis in these cases should be accepted with serious consideration especially when the author mentioned that the low voltage in some cases didn't return to normal and also one developed tachycardia and W. P. W. syndrome after operation where as the pre-operative tracing was normal.

In fact, the relationship between myocarditis and suppurative processes is well expressed by *Bailey* and *Anderson*[42] who said «The conclusion is that although there is no known etiology, the frequent association of the disease with infection especially with pyogenic infection of the skin is suggestive.» Burns have been suggested as a possible etiologic agent for isolated myotarditis by *Zuppinger.*[43] *Brenner*[44] also described a case of a 4 year old girl with serous myocarditis 17 days after burns of left hand. *Zinck*[45] in his exhausting and admirable discussion of the change of heart in burns stated that in the early stages there were marked hyperemia and slight increase of adventitial histiocytes together with swelling of the fibers and vacuolization along its long axis. There was also Zenker's degeneration with myolysis which occured as early as two hours after the burn and was sooner or later followed by vacuolization and disintegration, most marked after twenty six days. In the late cases, there was oustanding disappearence of parenchyma around the vessels, not only the small but also the larger ones, and it also showed periadventitial edema which came from lymph and blood serum through the dilated vessels. The edema is later followed by fibrous tissue and collapse of capillaries with a picture of fine sclerosis which was the same as that described by *Rössle*[21] with the diagnosis of «seröse myocarditis» mentioned above. Most important of all is that there was true myocarditis with histiocytic and lymphocytic infiltration in two of the cases reported by *Zinck* (one 3 year old and one 18 year old boy died 9 days and 7 hours after burns respectively).

3. Allergic hypersensitiveness to drugs etc.

Allergic conditions in connection with myocarditis were first called to attention by *Ecke*[46] who reported an 18 year old girl who died of diffuse myocarditis with acute pain in the upper abdomen for three days. Besides the change in the myocardium there was marked fatty degeneration of the liver and small cell infiltration of the kidney. The author believed that the changes were the result of allergic or hypersensitive conditions. However the true relationship was not established until *Nelson*[47] in 1934 and *Sikl*[9] in 1936 reported 1 and 2 cases respectively of eosinophilic myocarditis after injections of bismuth and arsenic compounds for syphilis. The cellular infiltration was chiefly eosinophilic although there were patchy necrois, a few tuberculoid infiltrations, and many myogenic giant cells. *Sikl* also mentioned that his case was the same as *Stoeckenius's*, reported earlier. Later *Brown* and *McMamara*[48] also reported a similiar case with myocarditis (55 % of the cellular infiltration is eosinophiles). *French* and *Weller*[49] in 1942 first described findings in the myocardium of 126 cases among 293 who had taken one or the other kind of sulfa drugs. There was significant interstitial myocarditis with eosinophilic leucocytes, which was however chiefly perivascular in distribution, although it also occured diffusely. They also described the presence of large mononuclear cells of clasmatocytic type and numerous characteristic cells with granular eosinophilic cytoplasm. In order to prove the relation between the myocarditis and sulfa drugs they did animal experiments by intraperitoneal injections and found 38 of the 60 mice and 33 of the 47 rats developed eosinophilic myocarditis while the controlled 29 mice and 26 rats did not have this finding. This finding seems very conclusive although it had been reported by *Angevine* and *Furth*[50] that in a certain strain of mice there was a peculiar disease with hemorrhage into the pleural cavity causing death, hemorrhage in the pericardium, endocardium and also testicles and cellular infiltration of polymorphonuclear leucocytes and monocytes in the myocardium in 23 of the 25 hearts examined. Also *More, McMillan* and *Duff*[51] reported in 1946 that among 375 patients who received sulfa drugs, in 2,000 autopsies there were 22 cases with lesions in various organs attributable to sulfonamides. There were 5 with granulomatous lesions in the heart with the appearence of Zenker's necrosis and 6 cases with interstitial inflammation of the heart. The cellular infiltration is chiefly monocytic but also neutrophilic and eosinophilic. However in some cases eosinophiles was absent. *Wells* and *Sax*[52] also reported a case who received 0.9 gm. of sulfadiazine three times a day for 16 days and also had «flue» for 10 days before he died four hours after the onset of illness. The role of hypersensitiveness in this case is very doubtful because the heart weighed 460 gm; too much in such a short course of 16 days. Moreover, there were only a few eosinophiles and also no change

of hypersensitiveness in other organs. In this connection the report of *Chafee, Ross* and *Gunn*[53] should also be mentioned. They found one of the six cases with a history of asthma in a total of 3,241 autopsy cases, had acute diffuse myocarditis with a large number of eosinpohiles and also necrosis while in another case there was non-suppurative myocarditis with collections of lymphocytes, plasma cells and a few eosinophiles. Myocarditis[54] had also been reported in a patient who died after taking Optalidon which consists of isobutyl allyl barbituric acid, pyramidon and caffeine, but again the role of hypersensitiveness in this case is doubtful because of the presence of only small lymphoctes, but no eosinophiles. In conclusion, there is ample evidence at present that drug hypersensitiveness or allergy is responsible for certain cases of acute diffuse myocarditis especially when large numbers of eosinophiles are present. In a recent report by *Jaffe*[55] the author claimed that 450 cases of myocarditis had been proved histologically, 44 % having syphilis, 48 % schistosomiasis and 28 % ankylostomiasis thus in 28 % the patient had more than one disease. The author didn't believe that the disease was caused by organisms or the ova (only in one case ova of schistosomiasis were found) and most of them were infected repeatedly so that a state of allergy existed.

4. Deficiency of vitamin B_1 and potassium.

Follis[56] et al. in their first paper mentioned that *Schrader, Prickett* and *Salmon* first described pathological alternations in the heart, kidney, pancreas and intestine of rats which had been placed on a diet deficient in potassiums and that *Thomas, Mylon* and *Winternitz* had confirmed the cardiac lesion although they failed to notice any change in other organs. The authors in their own experiments had noticed that the rats with low potassium diet showed changes in the heart 15 days after the beginning of experiments with loss of striations followed by karyolysis or karyorhexis assocated with emigration of leucocytes first, and mononuclear phagocytes later. In some animals the process took on the appearence of diffuse myocarditis with widely spread necrotic fibers surrounded by leucocytes and from the sixth week on the damage was gradually replaced by fibrosis and the lesion was much more marked in both ventricles. The same authors[57] in their later experiments had found, that 6 out of the nine pigs receiving a diet adequate in all known respects, except for its thiamin content, and 5 fed with desiccated liver known to be poor in thiamin but probably adequate otherwise as a source of the vitamin B complex, developed lesion consisting of focal or diffuse necrosis of myocardial fibers and such areas were infiltrated with leucocytes later on, and in the chronic cases it was replaced by connective tissue so that scar resulted. *Swank* and *Bessey*[58] also produced the similiar picture in pigeons which were deprived of thiamin. In addition there were EKG abnormalities and a decrease

of carboxylase content of the heart muscle. Clinically *Toreson*[59] reported a 15 year old boy who had a history of prolonged malnutrition, died of diffuse isolated myocarditis and the heart disease was known to have existed for at least six months, with severe progressive failure of the right heart, left bundle branch block and ventricular fibrillation before death. The author stated that it was possible that the myocardial lesions might have been incited by prolonged malnutrition and the lesions resembled those experimentally produced as described in the recent literature. It seems from the above description that the pathological picture of the myocardium in dietary defiency is primarily degeneration and necrosis and then followed by secondary cellular infiltration. Certainly more work should be done to ascertain whether the cellular infiltration is really inflammatory or just a reaction of the necrosis.

Symptoms, signs and course:

Idiopathic myocarditis occurs in all ages including infancy and childhood. However in the early literature, reported by *Bernheim-Karrer*,[36] *Riesenfeld*[60] and *Löwenthal*,[61] it was considered as being cases of status thymicolymphaticus with «metastasis of lymphocytes» in the myocardium from the lymphatic apparatus. Not until 1922 did *Rieder*[62] and also in 1923 *Bernheim-Karrer*,[37] consider that the myocarditis was responsible for the cause of death. Since then more cases of idiopathic myocarditis in infancy and childhood appeared in the literature including *Steiner's*[63] one case, *Maslow* and *Lederer's*[38] one case, *Smith* and *Stephens'*[26] first two cases and *Saphir's*[19] three cases (10 months, 15 months and 3 years old respectively). *Singer*[64] had also found 2 infants who died suddenly with myocarditis but he considered it might have been caused by a clinically overlooked infection, possibly diphtheria. Recently *Keller*[65] added six more cases of idiopathic myocarditis occuring in infancy and childhood.

Except cases that died suddenly, most remaining cases reported in the literature, present a picture of progressive or rather sudden onset of congestive heart failure for a few hours or a few months before the patient dies or recovers. They present cyanosis, dyspnea, drop of blood pressure, increase of frequency of respiration, weak and rapid pulse, and gallop rhythm. Edema and signs of congestion of internal organs are also present. Besides the above mentioned, *Smith* and *Stephens*[26] found conspicuous cardiac enlargement, particularly in the more chronic cases, premature contractions and pulsus alternans are quite common. *Bailey* and *Anderson's*[42] case had cardiac pain and in *Bonsdorff's*[6] 8 cases one had constriction over the chest with cold sweat and the other had sharp pain across the chest, both shoulders and on occasion down the arms (this patient had palpitation for two years which is rather unusual for

this disease). In *Wassmann's*[25] two cases one had pain behind the sternum with nausea, vomiting and a temperature about 40 degree C. which is not at all an usual picture in idiopathic myocarditis. Symptoms are usually more acute and fulminating in children. Among the reported cases as listed above the course usually lasted between 2 days to 2 weeks. In *Keller's*[65] paper vomiting, loss of appetite, pallor cyanosis of lips increase of respirations and finally tachycardia from 120—175 per minute are the common findings. *Saphir*[66] in his recent review of myocarditis in children had made an excellent statement: «clinically myocarditis should be considered when, during the course of infectious disease, the condition suddenly turns to worse without apparent cause. Tachycardia out of the proportion of the fever particularly accompanied by cyanosis is the early warning of myocarditis.» EKG findings have also been stressed by various authors in the diagnosis of this disease. The most usual findings are low voltage, isoelectric or inverted T waves in one or all the leads, and prolongation of the P-R interval *(Wassmann, Kjaerjarrd, Bonsdorff* etc.). *Kjaerjarrd*[27] also reported auricular fibrillation in his 4th and 5th cases that developed signs and symptoms of cardiac failure a few after a «cold». His fifth case also had ventricular extrasystoles. Auricular fibrillation was also present in *Bonsdorff's*[6] first and fifth cases. In two of his 8 cases (3rd and 5th) there was interventricular block and in one (4th) left bundle branch block. In this connection it is interesting to note that some of the authors reported cases of idiopathic myocarditis or myocarditis from infectious disease with little or non-characteristic cardiac symptoms and minor EKG findings as *Glatthaar's*[41] 28 cases which were supposed to be of focal infection in origin. The diagnosis of myocarditis in these cases should be accepted with serious consideration as the EKG tracings only showed inverted T waves in lead 1 and 2, prolongation of P-R interval to 0.24 second, low voltage or extrasystoles especially when 5 of them had only subjective improvement without demonstrable EKG changes and in 8 more cases neither clinical nor EKG improvement could be demonstrated after operation. Furthermore there was one case whose EKG was normal before operation but W. P. W. syndrome and tachycardia appeared 7 months after the tonsils were removed. It is of course wrong to consider prolongation of P-R interval greater than 0,2 second as normal in every case who is healthy and presents no present or past heart disease. Although *Longue* and *Hanson*,[67] *Grybiel* et al[68] and *Steward* and *Manning*[69] had reported prolongation of P-R interval greater than 0,21 second in 1. band 2,2 % of normal and healthy aviators respectively. We must still remember that many cases of acute myocarditis or idiopathic myocarditis are not recognized clinically; therefore observers collecting large series of routine EKG tracings will report certain percentages with

prolongation of P-R interval in apparent healthy individuals. However it is also erroneous to believe every case suffering from focal infection or other diseases with prolongation of P-R interval, associated without other abnormal findings or characteristic cardiac symptoms as a case of myocarditis when we consider that this finding, prolongation of P-R interval, can happen in other conditions besides myocarditis. Although *Walter*[70] tried to correlate the pulse rate and conduction time as a sign of myocarditis by tating that a prolongation of the P-R interval accompanying tachycardia is an early sign of myocarditis which differs with tachycardia of other origin such as following exertion in normal individual in that the latter is not accompanied by prolongation of the P-R interval. However even in myocarditis tachycardia following exertion is not necessarily associated with prolongation of the P-R interval and its value in helping the diagnosis of myocarditis is doubtful. In conclusion, the idiopathic myocarditis usually presents signs and symptoms of cardiac failure for variable periods and also findings in EKG tracings of myocardial damage and the possibility of such a disease should always be kept in mind when the above findings are evident. Considering the course of this disease, except in those who succumbed suddenly, most of the reported cases run either an acute fulminating course with marked cyanosis and rapid death or a more protracted one, which either leads to death after a period from weeks to months or recovery. A subdivision has been made by *Boikan*[71] who stated that the infection can happen only once with a disease precess finally healed, with formation of new connective tissue, but it can also advance to a clinical picture with degeneration of the myocardium and death, hence the term «myocarditis peniciosa» is applied. In between these two there are also cases characterized by the simutaneous presence of recent and old inflammatory processes which indicates the repeated infection of the myocardium by the unfamiliar obscure etiological agent etiology. He also stressed that the symptoms of this disease seldom apear until the late stages when anatomical changes results in death the progressive destruction undoubtly has reached its greatest extent.

Sudden death is not an unusual outcome of this disease. In fact many cases of sudden death with cellular infiltration in the heart had been put under the diagnosis of status thymicolymphaticus. As early as 1905 *Bernheim-Karrer*[36] had reported an eighteen months old child with no fever but a pulse rate of 220 per minute who died suddenly two days after illness. The heart was found to be infiltrated with round cells but he considered it a case of status thymicolymphaticus. In later years *Riesenfeld*[60] while reporting 5 cases from 9 months to one and one half years old who died sudden, ly or shortly after illness with pathologic findings of hypertrophy of the heart and hyperplasia of lymph apparatus all over the body including the thymus gland, stated that the round cell infiltration in

the heart of such cases reported by other authors was coming from the lymph apparatus in other parts of the body just like metastatic tumor cells. It is also interesting to notice that even as late as 1920 *Löwenthal*[61] reported a 16 months old child with cough, diarrhea and dyspnea for 10 days, who died suddenly on the day of admission and stated that the small round cell and plasma cell infiltration in the myocardium might be the result of hyperplasia of lymph follicles of the heart itself just like the enlargement and swelling of all the lymph apparatus elsewhere. This trend of thought however changed in 1922 when *Rieder*[62] reported nine children ranging from 3 months to 6 years old who died suddenly or shortly after illness in 6 cases, and trauma of the head in 3 cases with cellular infiltration, not only lymphocytes but also polymorphonuclear leucocytes, plasma cells and eosinophiles in the myocardium besides the enlargement of lymph apparatus including the thymus gland in 7 of the nine cases. This author expressed his belief that the cellular infiltration was due to actual inflammation and not part of the picture of status thymicolymphaticus. *Bernheim-Karrer*[37] in 1923 also changed his former belief and stated that the sudden death was due to the inflammation of the heart which was infiltrated with round cells when he reported a 13½ months old child who died 14 days after the onset of eczema of the face with exudation. From then on similar cases were reported including *Saphir's*[19] ten cases in 1942. *Helwig* and *Wilhelmy*[12] while reporting 3 cases that died suddenly stressed the opinion that interstitial myocarditis should receive serious consideration in any case of sudden and unexpected death in which, at autopsy, no anatomic lesion could be held responsible macroscopically. Similar conditions also occured in cases reported by *Gierke, Saltykow, Magner* and also *Sampson.* In an extensive study of sudden deaths in the U. S. army *Moritz* and *Zamcheck*[72] reported that among the 200—300 cases that suddenly died of heart disease, 14 belonged to subacute isolated myocarditis. The same importance had also been mentioned by *Munck*[73] who reported 6 cases of old myocardial fibrosis and one case with diffuse subacute myocarditis among 500 sudden deaths from heart disease.

CASE REPORT

Case 1. Autopsy No. 1395/47 (clinical data has been obtained from Bürgerspital with thanks) Patient, W. S., a ten years old girl, looked pale and weak and was not going to school for the past year. In September 1947 and earlier according to her, she had abdominal pains which always disappeared spontaneously. The pain was localized more or less in the right lower quadrant. No vomiting or diarrhea. On the morning of November 30th, 1947 she again complained of marked abdominal pain with the diagnosis of acute exacerbation of chronic appendicitis. She also had loss of appetite and vomiting once, and was then sent to Bürgerspital. In the family history, no tuber-

culosis or hereditary disease. Past history revealed that she had «measles» in childhood and «mumps» some weeks before the present illness. The stepmother knew the patient since she was two years old. There were no symptoms in the past suggesting pleurisy, disease of lung or kidney. The stepmother had never noticed any ascaris worm in the patient's stool. In 1946 however the girl had lesions on her face diagnosed as «impetigo». On admission the temperature was 38 degrees C. and the pulse rate was 125 per minute. Physical examination revealed a pale and somewhat nervous girl of normal development. Impetigo contagiosa was seen on the upper and lower lips. Tonsils were large but without apparent infection. Respirations were normal and regular. Heart was not enlarged and normal in configuration. Heart sounds were normal in tone and there were no murmurs heard. Impetigo contagiosa was also present on the left knee and left lower leg while on the right lower leg there was an old superficial traumatic wound. The abdomen was soft and there was slight resistance in the right lower quadrant especially near the upper half of McBurney's point. There was rebound pain in the R.L.Q. too, and with rectal examination pain was elicited over the R.L.Q. with combined palpation. The W.B.C. was 19,400 per c.mm. Urine was negative. A diagnosis of acute appendicitis was made and she was operated on the same day, Nov. 30th, 1947. The appendix was found to be free except near the distal end, without any swelling or injection. However there were many large mesenteric lymph glands. The diagnosis at the operation was lymphadenitis mesenterica although the appendix was found, on section, to have chronic inflammation with rich cellular infiltration, chiefly round cells, in the submucosa. The vessels were dilated and filled with polymorphonuclear leucocytes. There was no fever the day after operation and the pulse rate was 100 per minute. On the same afternoon the temperature rose to 37.5 degree C. It seemed that there was no complication, but in the afternoon of the second day after operation, her condition suddenly became worse with cough, imperceptible radial pulse, cold extremities, vomiting and marked tachycardia, 140—150 per minute. The doctor in charge thought of bronchopneumonia because some dullness was found over both lung bases. She died suddenly the same afternoon although her condition had been better for about one hour after coramine injections. An autopsy was done approcimately 16 hours after her death (only the important findings mentioned). On the upper and lower lips and also the left lower leg there was impetigo contagiosa mentioned in the physical examination. There were adhesions around the caecum and large intestine. In the pericardial cavity there was 100c.c. of somewhat, opaque yellowish fluid but the pericardium appeared glistering and smooth. The heart was somewhat enlarged, 190 gm. in weight (normally 120—150 gm.). Both the auricles and ventricles are dilated and the myocardium was flabby with many yellowish streaks (fig. 1). Some of them appeared in spots, varied from 1—3 mm. in diameter, and others confluented together. With formol fixation the streaks appeared in grayish white color in contrast with he darkish brown musculature. The apex on longitudinal section appeared as a big grayish white patch. The left ventricle measured 12 mm. and the right 4 mm. in thickness. All the valves and coronary vessels were intact. The lungs appeared congested and edematous and there was 100 c.c. clear yellowish fluid in both pleural cavities. The tonsils were enlarged but not cryptic or covered with membranes. The ovaries were of adult size, white and smooth and on cutting the tissue was darkish red and rich in blood.

Microscopic examination:

Liver: Atrophy due to congestion. The liver cells were rather small and showed fine fatty droplet degeneration, but no infection.

Fig. 1 (case 1) longitudinal cutting of the left ventricle showing the large patch of fibrosis in the apex and streaks on the anterior surface.

Fig. 2 (case 1) section from the left ventricle showing severe myocarditis with marked cellular infiltration and degeneration of muscle fibers. Hämalaun Eosin stain, Magnification x 75.

Spleen: Normal in appearence except the pulp was congested. Plasma cells were seen in the pulp but not in the follicles.

Kidney: Normal except marked congestion.

Ovaries: No infection but also marked congestion. They were rich in primordial follicles.

Femur bone marrow: Marked hyperplasia of all cellular elements. No infection either.

Lungs: Slight emphysema. No infection but there was desquamation of the epithelial lining of the small bronchi.

Heart: Although the pathological changes were severe and generalized, they were most intense, in the septum, and both ventricles. They were much less in the left auricle while in the right auricle the changes were negligible if compared with the septum. The transverse sections taken from the apex which on macroscopic examination had the most severe changes showed that the pathological changes involved the whole myocardium. However the transverse section of the left ventricle taken near the auriculo-ventricular junction showed that the changes were most marked near the pericardium and endocardium while in between the changes were much less intense. The changes could be described as cellular infiltration, changes in muscle fibers and interstitial tissues (fig. 2). The cellular infiltration consisted chiefly of lymphocytes, histiocytes and polymorphonuclear leucocytes. Occasionally very few eosinophiles and plasma cells were seen. There were infiltrations of inflammatory cells in the endocardium extending from the myocardium. There was fibrin collection with fibrous tissue around the vessels which appeared normal. The most remarkable feature was that in some places the cells filled up the spaces in between the widely separated muscle fibers together with fibrin, fibrous tissue, edema and occasionally the remnants of muscle fibers. The widely separated and clear spaces were very marked in some areas and interlaced with fibrous tissue, well shown by trichrome or Jaune Solide stain, and fibrin. Occasionally the whole widely separated space was devoid of anything. The muscle fibers were degenerated and thinner and appeared in different size with some very slender, either straight or tortuous. Some of them look like threads in between the extensive cellular infiltration together with short isolated remnants. However there was no vacuolization or loss of striation of the remaining fibers. In trichrome stain the sarcolemma of the entirely degenerated muscle fibers were also seen as thin empty outlines in between the fibrous tissue and cellular infiltration. The increase of interstitial fibrous tissue was best seen perivascularly and also in between the muscle fibers.

Anatomical diagnosis: Severe diffuse myocarditis with multiple fine myocardial degeneration. Marked dilatation of both, right auricle and ventricle. Edema of myocardium and hydropericardium. Slight interstitial edema of lungs. Hypostasis of lower lobes. Slight hydrothorax of both sides. Congestive tracheitis and bronchitis. Septic hyperplasia of spleen. Slight enlargement of the mesenteric lymph nodes and tonsils. Slight edema of the brain. Brown atrophy of liver parenchyma. Edema of kidneys. Impetigo contagiosa of the face and left lower leg. Hyperplasia of ovaries.

Summary: A ten years old girl, pale and weak, who had history of pain in the right lower quadrant and «impetigo contagiosa» for a few months and «mumps» a few weeks before the present illness. She died two days after appendectomy with marked tachycardia, vomiting, cold extremities and an imperceptible radial pulse. Histologically all the organs were normal except the heart had severe diffuse myocarditis with cellular infiltration chiefly lymphocytes, histiocytes and polymorphonuclear leucocytes, degeneration of muscle fibers and an increase of interstitial fibrous tissue.

Case 2. Autopsy No. E. 962/48. Patient, V. P., one year and one month old girl who was born on Jan. 14th. 1947. The birth was normal and the weight was 2,600 gm. Nothing pathological was found after birth and no murmurs were heard in the heart. In the first month after birth she had cyanosis while crying which however disappeared entirely after the 3rd month. The child was somewhat pale but otherwise normal. The feedings were normal and she never suffered from any disease except «bronchitis» for a short period when she was 3 months old and «otitis media» 14 days before her present illness. She never had gastro-intestinal disturbance or diphtheria before. The present illness started on February 11th, 1948 when her sister noticed that the child didn't eat any more and had some difficulty in breathing. No fever or respiratory symptoms. The next day the skin was found to be pale and somewhat cyanotic. The child was rather weak and the respirations were rapid. Her pulse was fast and weak but still regular. Physically the hearth was found enlarged on percusion, about one finger beyond the right border of sternum and midaxillary line on the left side. There was a gallop rhythm and the heart sounds were weak but no murmurs were heard. The breath sounds on the left lower back were bronchovesicular and louder and thought to be due to compression by the enlarged heart. The child died in the early morning of February 14th, 1948 in spite of treatment which consisted of cardiac stimuli as Benervam, percorten and Redoxen. On Postmortem examination the heart was dilated and weighed 50 gm. There were compression of the left lower lobe of the lungs and serous fluid in the left pleural cavity. The thyroid and thymus glands were enlarged. The trachea below the vocal cord was found to be covered with exudation which continued into the dilated bronchi. Both epicardium and pericardium were normal. Both the right and left ventricle were normal in thickness. The myocardium was normal grossly except the color was somewhat paler. No streaks or spots were seen.

Microscopic examination:

Trachea and bronchi: The epithelial lining was covered with exudation but no fibrinous inflammation was seen. There were many round cells and some segmented leucocytis infiltration in the epithelium and also the musculature layer.

Lungs: Very small pneumonic areas consisted chiefly of round cells and histiocytes and also inconspicuous foci with large cells containing many nuclei were seen. Some areas were rich in eosinphiles especially where the large cells were present. In the alveoli large cells, probably transformed from the alveolar lining, with acidophilic cytoplasm, and pale vesicular nuclei, were seen. The large cells with many nuclei were of foreign body origin (most probably the swallowed food). Besides this focus there were also atelectasis and slight thickening of the lung tissue. The hilus lymph nodes were very rich in blood and showed a picture of sinus catarrh.

Liver: Only acute hyperemia with slight brown atrophy but no fatty degeneration. Cells were widely separated with congestive atrophy.

Heart: The change was extensive. It was most intense in both ventricles and septum, less in the left auricle and negligible in the right auricle. The cellular infiltration was diffuse and consisted chiefly of plasma cells and histiocytes (fig. 3). Lymphocytes and polymorphonuclear leucocytes were also present. The muscle fibers showed old degeneration with some of them very thin, thread liked, and some tortuous. There was marked fibrous tissue replacement. There was also evidence of fresh degeneration with the disintegrated portion of the muscle fibers appearing as irregular pieces of acidophilic stained substance about the size of red blood corpuscles together with histiocytes and round cells filled up the emptied sarcolemma (fig. 4). There was also hydropic degeneration appearing as vacuoles along the long axis of the fibers near

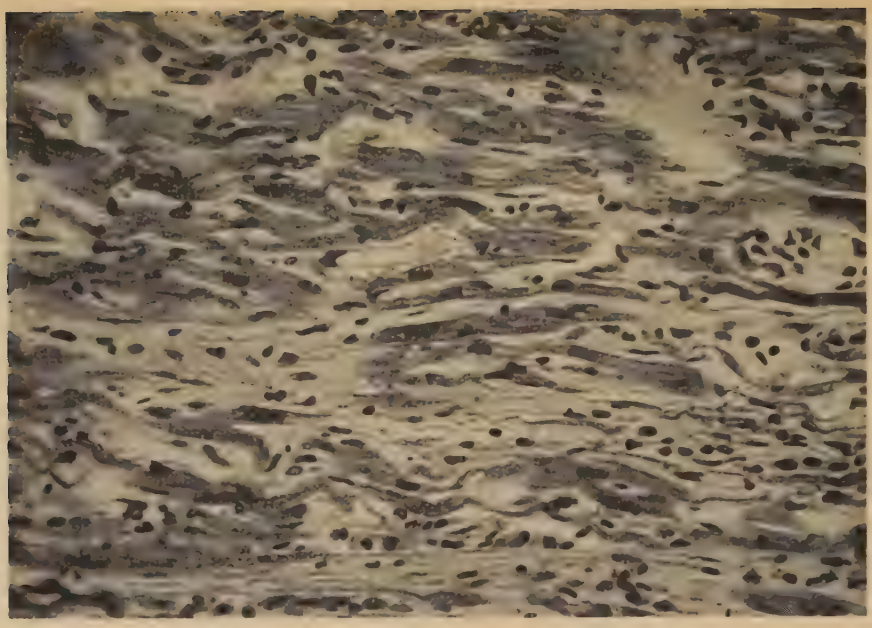

Fig. 3 (case 2) section of the heart showing cellular infiltration with histiocytes and round cells and degeneration of muscle fibers. Hämalaun Eosin stain. Magnification x 280.

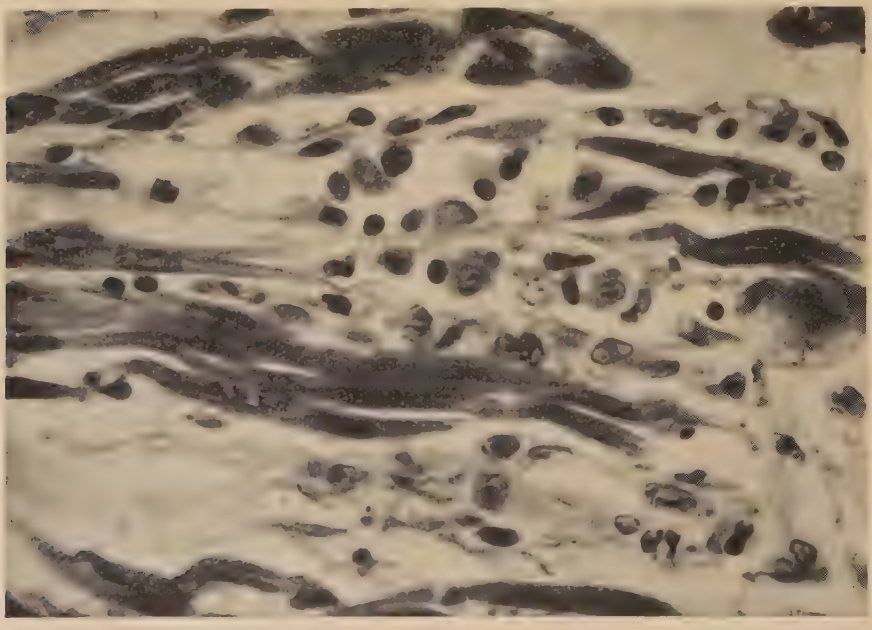

Fig. 4 (case 2) Higher power showing of muscle fibers with the empty sarcolemma filled up with histiocytes and round cells. Magnification x 630.

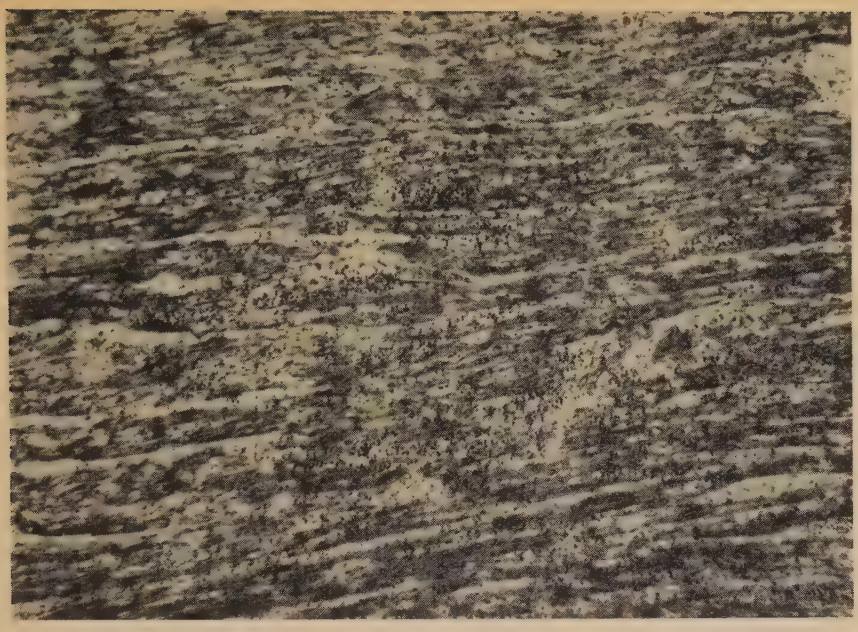

Fig. 5 (case 3) Section of the heart showing interstitial cellular infiltration. Note the more patchy distribution as compared with the first two cases. Magnification x 75.

the nucleus. By trichrome stain the interstitial fibrous tissue was increased. By Sudan III stain there was generalized fine fatty droplet degeneration in some areas. Edema was also present. Vessels were all normal without particular perivascular collection of inflammatory cells or fibrous tissue.

Anatomical diagnosis: Acute diffuse myocarditis with dilatation of both auricles and ventricles. Atelectasis of the left lower lobe and hydrothorax of the left pleural cavity. Small inconspicuous focal pneumonia of the lung. Hyperemia of the liver. Congestive and exudative tracheitis and bronchitis.

Summary: A one year and one month old girl who suddenly developed difficulty of breathing, pailler, cyanosis and rapid and weak pulse. Had «bronchitis» when she was 3 months old and «titis media» two weeks before her present illness. She died 3 days after the onset of symptoms. The only pathological finding was the acute diffuse myocarditis consisting of cellular infiltration, old and new degeneration of muscle fibers and increase of interstitial fibrous tissue.

Case 3. Autopsy No. 296/47 (clinical data has been obtained from Kinderspital with thanks). This was a seven months old girl admitted to Kinderspital in March 2nd, 1947 with a history of difficult breathing for two days. There was no hitory of tuberculosis in the family. One brother died at 7 months with «blood disease» from rectal hemorrhage. Another brother had been examined in the same hospital with the impression of «anemia». This child had a normal birth and the feeding history was normal. No disease of any kind was known in the past. Two days before admission there was difficulty with respiration but she was still active. On the following day the child laughed no more and the respirations became more difficult. She was

then actually dispneic. The father observed that child was quite pale although she had rosy cheeks before and for the whole following night the child was restless without any sleep. On the day of admission the temperature was 37.7 degree C. and there was foamy sputum from the mouth. She had vomiting on the day of admission and also the day before. The condition during admission was very bad although the appetite remained fair. On examination the child was found to be extremely pale and the eyes moved around constantly. Respiration was very difficult, rapid and shallow. The extremities were cold and the lips were cyanotic. In between the vaccination scars on the shoulder there were brownish spots of pin point size. No petechia seen. The conjunctivae and buccal mucosa were very pale. Lungs were normal. Heart was enlarged on percusion with tachycardia, 180 per minute but regular. Reflexes were all normal except the Brudzinski sign was suggestive positive. Laboratory findings revealed dark yellowish turbid urine which contained many R. B. C., W. B. C. and also hyaline cast. Hemoglobin was 72 % and the fluroscopic examination confirmed the enlargement of the heart to the left and also showed increase of lung markings. No sign of pneumonia was seen under the fluroscope. The child was given oxygen and cardiac stimuli but the condition became worse with cold extremities and coma and she finally died suddenly with convulsion 4 hours after admission.

The *autopsy* was done 17 hours after death. There was enlargement of liver one and one half fingers below the costal margin. The weight of liver and spleen was 205 and 31 gm. respectively. On the surface of the capsule of the thymus fine unquestionable hemorrhage was seen and the organ itself was three lobed, markedly enlarged and soft. On cutting the tissue appeared red. There was some clear serous fluid in both pleural cavities and on the pericardium there were a few pin point sized hemorrhages too. The heart was enlarged with dilatation of right auricle and right ventricle which had rather thin walls. The left ventricle was dilated too and there was also hypertrophy of its wall. On cutting the color of the myocardium was from brown to brownish yellow with yellowish streaks. The endocardium of the left ventricle was thickened. All the valves were dilated but free from pathologic changes. The lungs were small, grayish red in color and rather firm in consitency. On paravertebral cutting especially on the lower lobe small miliary grayish yellow foci were seen. The lymph follicles of the mouth organs were enlarged. The spleen on cutting was firm in consistency and showed very clearly recognized follicles. The kidneys were also big and firm on cutting, with a light brown color.

Microscopic examination:

Lungs: Some pneumonic infiltration with emigration of leucocytes in fine and separated areas. In the bronchi there were leucocytic accumulations. No giant cells were seen. There was desquamation of the bronchial epithelium. Increase of collagen fibers was present around the pulmonary vessels.

Spleen: The pulp was rich in blood. The Malpighi corpuscles were large and showed rich reticular elements and in some of them there was necrosis in the center with acidophilic staining necrotic material clearly seen under microscope. Together with the necrosis there was disintegration of the reticular cells too with pyknotic nucleus.

Kidneys: There were only slight cloudy swelling of the convoluted tubules and also fine fatty droplet degeneration of the parenchyma.

Liver: It showed diffuse fatty degeneration of the liver cells. Glisson's capsule was narrow and occasionally there was cellular infiltrations underneath the capsule. There was also edema with separation of liver cells.

Heart: The change was also a diffuse one with generalized cellular infiltration in both ventricles and septum while both auricles were not examined. The cellular infiltration consisted of polymorphonuclear leucocytes, histiocytes and lymphocytes. It was more patchy in appearence as compared with the first two cases (fig. 5). It had no special affinity around the vessels which were normal themselves. There was also degeneration of muscle fibers which appeared in different diameters. Some of the nuclei were larger and more vesicular in appearence. The change around the vessels was very conspicuous with an increase of collagen fibers and wide separation of muscle fibers. There was also a slight degree of increase of fibrous tissue in between the muscle fibers. The picture was chiefly a destructive one and the process was mostly only a few weeks old. No scars seen.

Anatomical diagnosis: Subacute diffuse myocarditis with marked dilatation of the whole heart and hypertrophy of the left ventricle. Chronic passive congestion of the lungs. Congestive bronchitis and also beginning of fine focal pneumonia. Congestive induration and hyperplasia of both liver and spleen. Congestive hemorrhage of the splenic capsule and the pericardium. Status thymicolymphaticus (?).

Summary: A seven month old girl who suddenly developed difficulty of respiration, pallor, restlessness, low grade fever, vomiting and tachycardia, 180 per minute. Cyanosis and cold extremities were also present. The child had never been sick before. The diffuse myocarditis was the only positive pathologic finding on autopsy with cellular infiltration, which was more patchy in appearence than the first two cases, degeneration of muscle fibers and increase of fibrous tissue in between the muscle fibers.

Case 4. Autopsy No. 542/46. This was a 36 year old housewife, small and rather fat. She enjoyed good health in the past until March 1946, two months after delivery, when she felt some difficulty in respiration. On examination she was rather pale with big «struma» on the thyroid region. The pulse was fast (not recorded) but regular. The heart sounds were normal with no murmurs heard. The blood pressure at that time was 150/80 mm. Hg. No edema was noticed. Besides the difficulty of breathing she felt rather tired. She was seen the second time on April 4th of the same year and felt better after rest and coramine treatment. However she had cough on his visit and was found to have an upper respiratory infection. There was no fever and the diagnosis were pharyngitis simplex and mild bronchitis. On May 16th she was examined again and the bronchitis was better but there was still some difficulty of breathing. Physical examination revealed emphysema of the lungs with prolonged and wheezing expirations. Pulse was good and the heart sounds were again normal. Struma was the same as before. «Bronchalen» was prescribed and the patient went back home in good condition. However the patient collapsed the next day (May 17th) with marked dyspnea, cyanosis and circulatory failure. The patient looked very anxious and the extremities were cold and she died shortly afterwards on the same day.

The *autopsy* was done 17 hours after death. It revealed a rather small sized woman but rather well nourished. The face was very cyanotic. Yellowish fluid was seen coming out from the nose. On the right lower extremity there was a 2 cm. long scar on the external malleolus. The breasts were found lactating. Small size thymus (20 gm.) was still present. The heart was not enlarged, only 290 gm. in weight. The right heart was not enlarged and both pulmonic and tricuspid valves were normal. Foramen Ovale was closed. The mitral and aortic valves were also normal with normal chordae tendinae and papillary muscles. The coronary arteries were normal except here and there tiny yellowish streaks were seen. The left ventricle measured 15—16 mm. in

thickness and on cutting the color was brownish red. No streaks or discoloration were seen. The aorta was absolutely free from atherosclerotic changes. In the trachea and large bronchi there was much mucous and the mucous membrane was darkish red. The thyroid gland was about the size of an adult's fist. The left and middle lobes were having had more nodules, while the right lobe was quite cystic. The whole thyroid compressed on the middle part of the trachea. The lung tissue was red with reddish foamy fluid coming out on cutting. The small bronchi also had darkish red mucosa and there was also grayish red mucous in the lumen. No focus of consolidation or emphysema was seen. The lymph gland in the hilum and trachebronchial area was not enlarged. The spleen was very much enlarged, measured 14,5×8,5×2 cm. It was flabby and soft and on cutting the pulp was very rich in blood. Many rather large follicles were seen. It weighed 265 gm. The liver was also enlarged and weighed 2,570 gm. It was also flabby and on cutting the tissue was rich in blood and swollen. The gall-bladder, adrenal glands and kidneys were normal except the last organ had fine cysts on both sides. The urinary bladder had a small diverticulum on the right half. The uterus had darkish red congested mucosa. The brain was rather edematous with normal meninges. The gastrointestinal tract was normal except the mucosa of the stomach was swollen and in the fundus there was many darkish red hemorrhagic spots.

Microscopic examination:

Hypophysis: Marked basophilic cells predominated and very few eosinophilic cells were seen. There were many chief (chromophobic) cells and the tissue was rich in blood.

Trachea: Round cell infiltration was very marked in the epithelium with some histiocytes, few polymorphonuclear leucocytes and plasma cells. On the surface of the epithelial lining many cocci were seen. The vessels were all dilated. The infiltration in most instances showed continuation through the epithelium and around the mucous glands.

Hilus lymph glands: Marked anthracosis was seen.

Lungs: Marked congestion and edema. No inflammatory change was seen. The large bronchus showed catarrhal bronchitis. There was no change to speak of bronchial asthma. The bacterial flora of the bronchus was chiefly of the non-characteristic group.

Spleen: It was much congested and the follicles were rather small. No cells of foreign origin or hemosiderosis were seen.

Thyroid gland: The nodule of the middle lobe was of colloid adenoma with cystic formation and it was rich in inflammatory cells (chiefly round cells) and fibrous reaction. The thyroid tissue was diminished.

Kidneys: Here and there in Henle's loop there was fatty degeneration. In the lumen of the excretory tubules there was much protein material. There was no change seen in the glomeruli. No glycogen was recognized in the small arteries. With Sudan III stain no arteriosclerosis was seen. In paraffin preparations there was some swelling of the main part of tubules in favor of nephrosis but it might be a postmortem change.

Liver: There was diffuse globular fatty degeneration. In Glisson's capsule there was some round cell infiltration, all lymphocytes. Glycogen was very little, only found here and there in the lobules.

Heart: Left ventricle had marked brown atrophy with lipofuchsin accumulation. There were only a few histiocytes and round cell infiltration interstitially, especially around the vessels but nodular formation was never found. Many elongated and slender cells (fibroblasts) were seen interstitially too. The fibrous tissue around the vessels was slightly increased. There was no apparent degeneration of the muscle fibers and some

of them appeared wider in diameter (hypertrophy). Some of the nuclei were bigger and richer in chromatin so that they stained darker. All the capillaries were filled with blood and congested. All the vessels were intact. The change in the septum was most interesting. Besides the above findings there was fibrous scars replacing the destroyed muscle fibers especially toward the endocardium which was much thickened. The His bundle underneath the endocardium of the septum near the bifurcation, especially around the left main branch, was surrounded by fibrous tissue and also cellular infiltration chiefly round cells. The bundle fiber itself was also vacuolated and degenerated. The nucleus of the bundle fiber was much elongated and knotty in appearence. Those degenerated bundle fibers stained much paler, light pinkish, as compared with the normal which was red in «Hematein Eosin» stain. The fibrous scar was more in those areas of septum where the consistency was firmer. The right ventricle however was free from any change except brown atrophy and a few fibroblasts.

Anatomical diagnosis: Acute cardiac insufficiency with chronic myocarditis and marked hyperemia of all the organs. Dilatation and slight hypertrophy of the right ventricle. Terminal edema of the lungs. Severe subacute tracheitis and exudative bronchitis. Maked edema and cloudy swelling of the liver. Swelling and hyperemia and also follicle hyperplasia of the spleen. Thymus persistens. Mamma lactans. Apoplexia uteri and edema of brain.

Summary: A 36 year old housewife with large struma dereloped difficulty of respiration two and one half months after a normal delidery. She suddenly died two months later. Had a history of pharyngitis and bronchitis after the onset of difficulty of breathing. The heart had a few fibroblasts and histiocytes only; there was much fibrosis around the His bundle fibers which were degenerated and stained lighter as compared with the normal ones. Other organs were normal.

Case 5. Autopsy No. 774/47. This was a sixteen year old boy, named R. H. He had never been sick before except he was told by a doctor while he was in the primary school that he should not do heavy exercise possibly because of heart trouble when he was 10 years old. He was working in a factory which was 7 kilometers from his home and he usually travelled by bicycle. The road was rugged and thus in some sections he had to exercise strenuously. According to the family he was very strong, athletic and did much gymnastic work. On the very day of his death he came home from the factory and dropped dead suddenly, on the road.

The *autopsy* was done 19 hours after death. It revealed a young boy with a body weight of 72 kilograms. The musculature was very well developed and proportional over the whole body including the chest and abdominal muscles. There was rather marked distention of the large intestine. Slight adhesions were seen between the left apex and pleural cavity. The thymus gland weighed 26 gm. There was 20 c.c. of clear fluid in the pericardial cavity. The heart was enlarged and weighed 520 gm. The right heart was flabby and dilated and the right ventricle was 5 mm. in thickness. Both pulmonic and tricuspic valves were normal. The left ventricle was also very dilated and its wall measured 20 mm. in thickness. Both aortic and mitral valves were normal. On cutting, the heart muscle was brownish red in color with no spots or streaks seen. Both the pericardium and coronary vessels were normal too. The lungs were much congested with blood and on cutting the color was dark grayish red. In the paravertebral part it was angrily red. The bronchus was not congested or swollen but contained reddish foamy fluid. The hilus lymph nodes were small, grayish red to black in color. The spleen was slightly enlarged, measured $17 \times 10 \times 5$ cm.

It was darkish red on cutting and the follicles were very difficult to recognize. The pulp was very rich in blood. The liver was also congested. The adrenal gland was rather small especially the left one, only 2.3 gm. in weight while the right one weighed 4.5 gm. The cortex was narrow. The urinary genital and gastrointestinal systems, were normal. The brain was normal. After formol fixation the septum of the heart was found to be much thickened, about 3 cm. in thickness. In its middle, anterior as well as posterior, and inferior parts there were many large whitish star shaped scars.

Microscopic examination:

Kidney: Normal except marked congestion.

Liver: Only passive congestion.

Lungs: There was marked congestion with R. B. C. filling up some of the alveoli. The bronchi showed desquamation of the epithelium but no inflammatory cells. There was marked edema too.

Thymus gland: The thymus was rich in Hassal's bodies which were calcified in some places. The in between tissue was thickened. Here and there fat tissue was seen mixed with the supporting tissue. It was also much congested.

Spleen: The pulp was rich in blood. Follicles were small and no special change was noticed.

Tonsils: The lymph apparatus was relatively proliferated and always separated by fibrous tissue in which there was some round cell infiltration. Round cells were also seen perivascularly in the capsule. There was one big cryptic cyst but no sign of rheumatic fever as the formation of collagen fiber from the exudation was seen.

Heart: There was no fatty degeneration or brown atrophy. The pathologic change was most severe in the septum, less in the left ventricle and least in the right ventricle while in both right and left auricles the change was negligible. The change consisted chiefly of marked increase of fibrous tissue, replacing the degenerated muscle fibers. The fibrous tissue was also increased in between the apparently normal fibers and around the vessels. The increase of fibrous tissue was especially marked in the septum where it appeared as a big patch. The muscle fibers in some places were thinner but some of them in the left ventricle and septum were hypertrophied with wider diameter and bigger nuclei which were richer in chromatin and stained darker. The vessels were normal except in the septum where narrowing of the lumen was seen probably due to contraction of the fibrous tissue or postmortem change. On transverse section of the left ventricle the incease of fibrous tissue was more in the middle part of the myocardium and less toward the pericardium and endocardium. The cellular infilration was very little with only a few small round cells and histiocytes. No polymorphonuclear leucocytes were seen. His bundle fibers were apparently normal in appearence The picture was chiefly one of myofibrosis, the end result of myocarditis some time ago.

Anatomical diagnosis: Chronic myocarditis with myofibrosis. Dilatation and hypertrophy of the heart. Passive congestion of all the organs. Adhesion of left apex. Edema of lungs. Chronic tonsillitis.

Summary: A 16 years old boy who had never been sick before dropped dead on the road suddenly while he was riding a bicycle. The heart was much hypertrophied with extensive fibrous tissue scar in the septum and few, round cell and histiocytes infiltration interstitially. His bundle fibers appeared normal.

Comment:

Pathologically our five cases can be divided into two groups. In the first three cases the change is chiefly destructive and acute with marked cellular infiltration and degeneration of muscle fibers. The cellular infiltration consists more of lymphocytes and plasma cells in two cases and polymorphonuclear leucocytes in one case although histiocytes and fibroblasts are also present. In all these cases, degeneration of muscle fibers is a dominent feature, either there is appearence of hydropic degeneration (vacuolization) along the long axis of the muscle fiber, or they appear in different diameter. In the more extensive ones the muscle fibers disintegrate into small tiny fragments remaining in the empty sarcolemma which is filled up with histiocytes and round cells. In the later stage all the fragments are carried away leaving the empty sarcolemma alone. There is no evidence that the muscle fiber degeneration is due to compression by the cellular accumulation as there are places where perfectly normal looking muscle fibers are surrounded by cellular infiltration. Fibrosis is not a prominent feature in these three cases although it is somewhat increased either around the vessels or in the interstitial space. However in the second case, there is a fairly conspicuous increase of collagen fibers around the vessel but in all these three cases there is no change of the vessel itself microscopically. Slight interstitial edema is present and it seems to us that some of the muscle fibers are also edematous and swollen. Changes of the nucleus are only observed in the third case of this group; some of them look bigger and more vesicular while others are smaller and deeper staining. No scar is seen. It is our belief that changes in these three cases are only a few weeks old. In the last two cases the pathologic picture is entirely different with myofibrosis predominating. We have no doubt that these two patients previously had some kind of myocarditis, most probably the idiopathic type, but either the condition is not diagnosed clinically, or the condition is too mild or subclinical to escape the patient's notice. In the first case (case 4) there is definite evidence that the bundle of His underneath the endocardium in the septum just below the bifurcation, especially around the left main branch, is surrounded by much fibrous tissue and also much more cellular infiltration as compared with only a few in other places. The bundle fiber itself is also vacuolated and degenerated with elongated and knotting nuclei. In the last case although the bundle of His appears normal there are many more and larger scars in the septum which even appear as large patches in some places.

In cases 1, 2 and 5 when we had a chance to make various sections of the whole heart including both auricles, we were surprised by the negligible or very slight changes in the right auricle, while the left au-

ricle although also very much less than both ventricles and septum, had more marked changes. This difference of distribution of pathologic changes is not mentioned in most of the reported cases. *Luscher*[74] in reporting two cases of tuberculous myocarditis had also noticed that the change is much less in the right auricle. It is a known fact that in virus diseases as anterior poliomyelitis, vitamin deficient diseases as beriberi and in intoxications as lead poisoning the pathologic a changes usually occur first and are also most severe in those parts where the metabolism is highest as the leg and arm muscles. Therefore we can also assume that the same explanation may be applied in this difference of pathologic changes between the auricles and ventricles which no doubt, have a much higher metabolism than the former.

Concerning the etiology our first case had a history of «impetigo» for quite a few months, then abdominal pain which was diagnosed as acute appendicitis, for at least two months, and finally, «mumps» a few weeks before the present illness. It is pretty difficult to ascertain the exact nature of the etiology since all these three conditions each might be responsible for the pathologic a changes in the myocardium. The second case had a history of «otitis media» which had been mentioned by *Wassmann*[25] as the cause in one of his cases, two weeks before the onset of the present illness. The third case is an extraordinary one, with no known disease occuring anytime before the onset of the symptoms of myocarditis. This is not at all rare in young infants as it had been reported by *Rieder*[62] and *Keller*.[65] The fourth case had a normal delivery two months before the onset of symptoms of difficult breathing and fatigue. Difficult breathing was thought to be due to compression of the very enlarged struma. The patient also had symptoms of upper respiratory infection which was diagnosed by the attending physician as «pharyngitis simplex» and «mild bronchitis» after the onset of difficult breathing. Although the last mentioned condition can well produce idiopathic myocarditis as has been discussed under etiology the pathologic picture speaks against this possibility since the upper respiratory infection or bronchitis occured only 5—6 weeks before death and yet the marked myofibrosis and the rather little cellular infiltration surely indicate that the process is at least of a few months, if not years. This patient had a fairly big struma which had round cell infiltration under microscopic examination. Although diseases of the thyroid gland as hyperthyroidism had been connected with diffuse idiopathic myocarditis the certainty of their relationship is very doubtful as *Saphir*[75] in his extensive review of myocarditis stated that there are no consistent inflammatory change in the myocardium of patients who die of hyperthyroidism. The fact that this patient had a delivery five months before death is most interesting. *Gouley, McMillan* and *Bellet*[76] had described seven cases

(four died and three recovered) of progressive cardiac failure following puerperium or miscarriage. These cases are characterized clinically by chronic cardiac decompensation, gallop rhythm, low voltage and inverted T waves in various leads in EKG tracings and microscopically disintegration of the myocardial fibers involving the nuclei to a lesser extent so that the latter remains as a conspicuous and often the major element in the cellular collection that has replaced the myocardium. Hemorrhage is common in these cases and there are moderate amount of lymphocytes and macrophages, occasionally neutrophiles and also eosinophiles. The same author cited that William had claimed that 1.5 % of cardiac death during pregnancy and soon after puerperium are the result of an «idiopathic myocarditis». It is therefore reasonable to think that this case might well be due to pregnancy or puerperium. The interval of five plus months between the delivery and death supported by the microscopic finding also favors this possibility. In the last case the etiology is again unknown but as said above, it is the end result of previous idipothic myocarditis either the infection is subclinical or the condition is not recognized clinically.

As the symptoms and signs are concerned our cases coincide with those reported by others. Pallor, dyspnea, cyanosis of lips, vomiting, and marked tachycardia are common among the infants and children. Loss of appetite although it had been emphasized by *Keller*[65] is not particularly so in our cases. Fever is not an outstanding feature, the first had a temperature of 38 degree C., the second normal and the third 37.7. Unfortunately all these cases ran a very short course and no detail laboratory studies and EKG tracings were done. All the three cases with predominantly cellular infiltration and degeneration of muscle fibers had a very short course. One died two days after appendectomy with no complications and the other two died two days after the onset of illness. No doubt the term «myocarditis perniciosa» of Boikan[71] can be applied here.

Concerning the last two cases who died suddenly we believe at least the first, a housewife of 36 years old, is due to fibrosis and more marked cellular infiltration around the left main branch of His bundle, which also shows degeneration of the fibers with elongated and knotting nucleus and much lighter staining, causing the interference of the conduction system. This point is further convinced by the normal weight of the heart, only 290 gm. although the blood pressure is in the highest normal level, 150/90 mm. Hg. The second case, a boy of 16 years old, although has no gross change of the His bundle, the very marked fibrosis in the septum and also especially surrounding the bundle fibers should also be considered as the possible explanation for his sudden death. However in this case the heart has enlargement and hypertrophy, 520

gm. in weight, and the left ventricle measured 20 mm. in thickness therefore acute heart failure should also be considered besides the interference of the conduction system as the cause of sudden death. It is surprising to notice how often the case is reported to have sudden death and yet so little attention and research have been paid to the conduction system. It is therefore well to keep in mind the possibility of an interference of conduction system as the cause of sudden death especially in cases when the chief finding is myofibrosis and the heart is not hypertrophied and enlarged.

Summary:

1. Five cases of the so-called idiopathic myocarditis are reported, three with more cellular infiltration and 2 with more myofibrosis.

2. The possible etiology of this disease is reviewed especially its relationship with virus infection.

3. Pathologically. lesions are much more extensive in the ventricles and septum while in the right auricle they are negligible. Possible explanation is discussed.

4. Sudden death among these cases are emphasized and the role of interference in the conduction system is evident in one of them.

Zusammenfassung:

Es wird über fünf Fälle von sogenannter idiopathischer Myokarditis berichtet, wobei in drei Fällen zellige Infiltrationen, in zwei Fällen fibröse Umwandlungen im Vordergrund standen.

Die ätiologischen Möglichkeiten dieser Krankheit werden untersucht, insbesondere der Zusammenhang mit Virusinfektion.

Es wird gezeigt, dass die pathologischen Veränderungen weit stärker im Gebiete der Kammern und des Septums ausgeprägt sind, während der rechte Vorhof praktisch frei von solchen ist. Es wird versucht, eine Erklärung für diese Tatsache zu geben.

Plötzliche Todesfälle bei diesen Fällen werden hervorgehoben; in einem der Fälle ist eine Beteiligung des Reizleitungssystems offensichtlich.

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